



# STIC Search Report

## Biotech-Chem Library

STIC Database Tracking Number: 10/600446

**TO:** Shobha Kantamneni

**Location:** 2c29 / 4b18

**Art Unit:** 1617

**Tuesday, September 19, 2006**

**Case Serial Number:** 10/600446

**From:** Noble Jarrell

**Location:** Biotech-Chem Library

**Rem 1B71**

**Phone:** 272-2556

**Noble.jarrell@uspto.gov**

Search Notes

## Scientific and Technical Information Center

## SEARCH REQUEST FORM

Requester's Full Name: SHOBHA KANTAMneni Examiner #: 80397 Date: 09/18/06  
 Art Unit: 1617 Phone Number: 2-2930 Serial Number: 106004446  
 Location (Bldg/Room#): 2C29 (Mailbox #): 4B19 Results Format Preferred (circle):  PAPER  DISK  
 \*\*\*\*\*

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Antimalarial activities and therapeutic properties of  
centrifugine analogue  
 Inventors (please provide full names): Suping Jiang; Thomas Hudson; Wilbur Milhouse

Earliest Priority Date: \_\_\_\_\_

## Search Topic:

*Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.*

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please do structure search for quinazolinone  
 Compounds as in claims 7, 12, 17, 22, 27, 32, 37, 42  
 and 62, 67. (claims attached).

Thanks  
 Shobha

JHR  
 JUNE 11 2007  
 SEARCHED INDEXED  
 GROUP 107

2 month fnd.

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## STAFF USE ONLY

Searcher: Mable  
 Searcher Phone #: \_\_\_\_\_  
 Searcher Location: \_\_\_\_\_  
 Date Searcher Picked Up: 9/18/06  
 Date Completed: 9/19/06  
 Searcher Prep & Review Time: 25  
 Online Time: 37

## Type of Search

NA Sequence (#)  
 AA Sequence (#)  
 Structure (#)  
 Bibliographic  
 Litigation  
 Fulltext  
 Other

## Vendors and cost where applicable

STN  Dialog  
 Questel/Orbit  Lexis/Nexis  
 Westlaw  WWW/Internet  
 In-house sequence systems  
 Commercial  Oligomer  Score/Length  
 Interference  SPDI  Encode/Transl  
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STRUCTURE FILE UPDATES: 18 SEP 2006 HIGHEST RN 907539-37-1  
DICTIONARY FILE UPDATES: 18 SEP 2006 HIGHEST RN 907539-37-1

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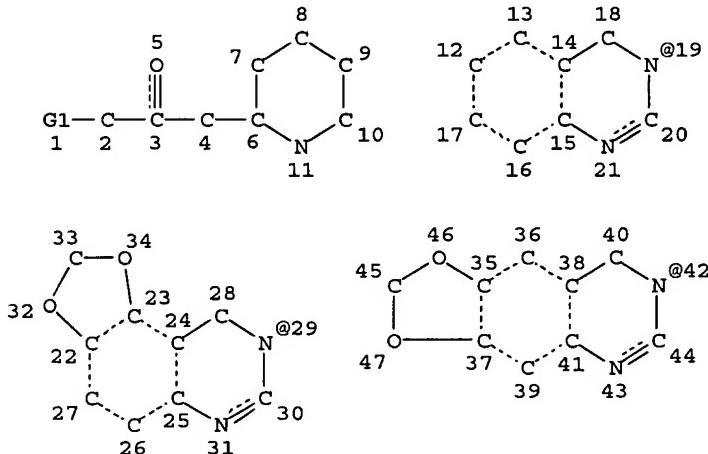
TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

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<http://www.cas.org/ONLINE/UG/regprops.html>

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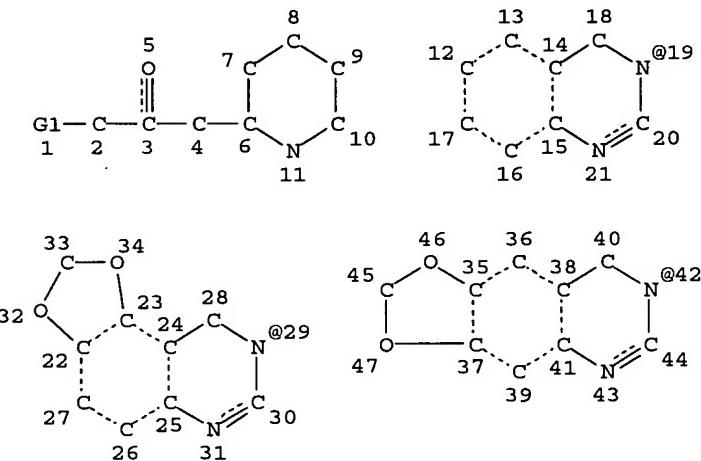
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NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE  
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FILE LAST UPDATED: 18 Sep 2006 (20060918/ED)

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L21 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:229598 HCAPLUS  
DN 142:348229  
TI Antimalarial activities and therapeutic properties of febrifugine analogs  
AU Jiang, Suping; Zeng, Qiang; Gettayacamin, Montip; Tungtaeng,  
Anchalee; Wannaying, Srisombat; Lim, Apassorn; Hansukjariya, Pranee;  
Okunji, Christopher O.; Zhu, Shuren; Fang, Dache  
CS Departments of Parasitology and Medicinal Chemistry, Walter Reed Army  
Institute of Research, Silver Spring, MD, 20910, USA  
SO Antimicrobial Agents and Chemotherapy (2005), 49(3), 1169-1176  
CODEN: AMACQ; ISSN: 0066-4804  
PB American Society for Microbiology  
DT Journal  
LA English  
AB Febrifugine is the active principal isolated 50 years ago from the Chinese herb chang shan (*Dichroa febrifuga* Lour.), which has been used as an antimalarial in Chinese traditional medicine for more than 2,000 years. However, intensive study of the properties of febrifugine has been hindered for decades due to its side effects. We report new findings on the effects of febrifugine analogs compared with those of febrifugine extracted from the dry roots of *D. febrifuga*. The properties of the extracted febrifugine were comparable to those obtained from the standard febrifugine provided by our collaborators. A febrifugine structure-based computer search of the Walter Reed Chemical Information System identified 10 analogs that inhibited parasite growth in vitro, with 50% inhibitory concns. ranging from 0.141 to 290 ng/mL. The host macrophages (J744 cells) were 50 to 100 times less sensitive to the febrifugine analogs than the parasites. Neuronal (NG108) cells were even more insensitive to these drugs (selectivity indexes, >1,000), indicating that a feasible therapeutic index for humans could be established. The analogs, particularly halofuginone, notably reduced parasitemias to undetectable levels and displayed curative effects in *Plasmodium berghei*-infected mice. Recrudescence of the parasites after treatment with the febrifugine analogs was the key factor that caused the death of most of the mice in groups receiving an ED. S.c. treatments with the analogs did not cause irritation of the gastrointestinal tract when the animals were treated with doses within the antimalarial dose range. In summary, these analogs

appear to be promising lead antimalarial compds. that require intensive study for optimization for further down-selection and development.

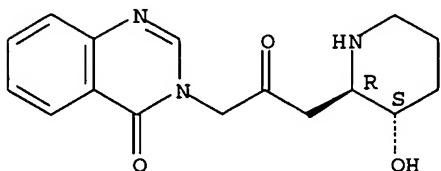
IT 24159-07-7, Febrifugine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antimalarial activities and therapeutic properties of febrifugine analogs)

RN 24159-07-7 HCPLUS

CN 4(3H)-Quinazolinone, 3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 24159-07-7, Febrifugine 55837-20-2, Halofuginone

640272-17-9, WR 222048 640272-18-0, WR 139672

640272-19-1, WR 059421 640272-21-5, WR 140085

640272-22-6, WR 090212 640272-23-7, WR 146115

640272-26-0, WR 088442

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antimalarial activities and therapeutic properties of febrifugine analogs)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 2 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2004:2702 HCPLUS

DN 140:70980

TI Antimalarial activities of febrifugine analogues

IN Suping, Jiang; Thomas, Hudson H.; Vilbur, Milhous K.

PA U.S. Army Medical Research and Material Command, USA

SO PCT Int. Appl., 66 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO2004000319	A1	20031231	2003WO-US20954	20030620 <--
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RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU2003251769	A1	20040106	2003AU-0251769	20030620 <--
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US2004053950	A1	20040318	2003US-0600446	20030620 <--
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PRAI 2002US-390334P P 20020620 <--

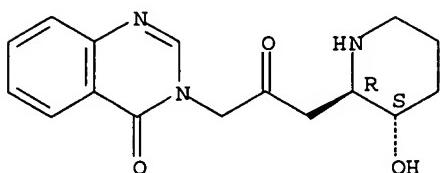
2003WO-US20954 W 20030620

AB Malaria is the most severe tropical parasitic disease that has caused millions of deaths in many countries. The threat of growing drug-resistant parasites requires development of new antimalarial drugs to overcome the emergence of resistance and to control the disease.

Febrifugine is the active principle extracted from the Chinese herb Chang Shan (Dichroa febrifuga Lour) that has been used to treat malaria for more than two thousand years. Studies on the efficacy have been hindered due to the emetic effects of febrifugine. The present invention discloses febrifugine, halofuginone and febrifugine derivs. for use as antimalarial agents without the severe emetic effects observed in direct herbal use.

IT 24159-07-7, Febrifugine  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antimalarial activities of febrifugine analogs)  
 RN 24159-07-7 HCAPLUS  
 CN 4(3H)-Quinazolinone, 3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 24159-07-7, Febrifugine 55837-20-2 640272-16-8  
 , Febrifugine XXX 640272-17-9, WR 222048 640272-18-0,  
 WR 139672 640272-19-1, WR 059421 640272-21-5, WR  
 140085 640272-22-6, WR 090212 640272-23-7, WR 146115  
 640272-26-0, WR 088442 640272-27-1, WR 059424  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antimalarial activities of febrifugine analogs)  
 RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr retable l32 tot

L32 ANSWER 1 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2006:100738 HCAPLUS  
 DN 144:198849  
 TI Novel dosage form comprising modified-release and immediate-release active ingredients  
 IN Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar  
 PA India  
 SO U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.  
 CODEN: USXXCO

DT Patent  
 LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US2006024365	A1	20060202	2005US-0134633	20050519 <--
	IN---193042	A	20040626	2002IN-MU00697	20020805 <--
	US2004096499	A1	20040520	2003US-0630446	20030729 <--
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	2002IN-MU00699	A	20020805	<--	
	2003IN-MU00080	A	20030122		
	2003IN-MU00082	A	20030122		
	2003US-0630446	A2	20030729		

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process

for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared. The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

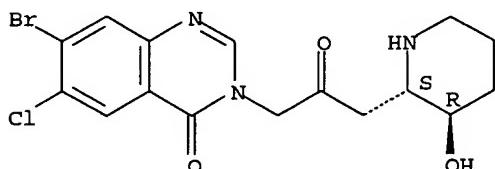
IT 64924-67-0, Halofuginone hydrobromide

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(novel dosage form comprising modified-release and immediate-release active ingredients)

RN 64924-67-0 HCPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, monohydrobromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HBr

L32 ANSWER 2 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2005:672608 HCPLUS

DN 143:159586

TI Drug-eluting device chemically treated with genipin

IN Sung, Hsing-wen; Chen, Mei-chin; Liang, Hsiang-fa; Tu, Hosheng

PA Taiwan

SO U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 211,656.

CODEN: USXXCO

DT Patent

LA English

FAN.CNT 12

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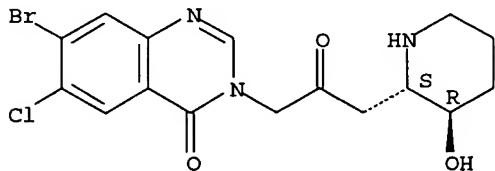
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2004US-574501P	P	20040526	
2004US-585775P	P	20040706	
2004US-0916170	A2	20040811	
2004US-0024101	A2	20041228	

AB A method for treating a target tissue of a patient comprises, in combination, mixing a drug with a solid-forming biol. material, chemical treating the drug with the biol. material with a crosslinking agent, loading the drug-containing biol. material onto a medical device, solidifying the drug-containing biol. material; and delivering the medical device to the target tissue for treating the tissue. Thus, a chitosan solution was adjusted to approx. pH 5.5, and a drug was added to the solution. This was loaded onto a stent, and the device was treated with genipin.

IT 55837-20-2, Halofuginone  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (drug-eluting device treated with genipin)

RN 55837-20-2 HCAPLUS  
 CN 4 (3H)-Quinazolinone, 7-bromo-6-chloro-3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

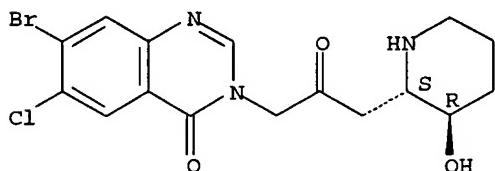


L32 ANSWER 3 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2005:497471 HCAPLUS  
 DN 143:32422  
 TI Crosslinkable biological material and angiogenic agent for promoting angiogenesis  
 IN Sung, Hsing-Wen; Liang, Huang-Chien; Tu, Hosheng  
 PA Taiwan  
 SO U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. Ser. No. 408,176.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 12

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	2004US-547935P	P	20040226	
	2004US-552517P	P	20040312	
	1997EP-0947356	A3	19971104	<--
	2004US-565438P	P	20040426	
	2004US-574501P	P	20040526	
	2004US-0610391	A	20040630	
	2004US-585775P	P	20040706	
	2004WO-US37217	W	20041105	
AB	A method for promoting angiogenesis in a patient comprising providing crosslinkable biol. solution to the target tissue, wherein the crosslinkable biol. solution is loaded with at least one angiogenic agent. In one embodiment, the at least one angiogenic agent is a non-protein factor selected from a group consisting of ginsenoside Rg1, ginsenoside Re, combination thereof and the like. In another embodiment, the crosslinkable biol. solution of the present invention is broadly defined in a form or phase of solution, paste, gel, suspension, colloid or plasma that may be solidifiable thereafter. For example, to increase pore sizes and porosities within test samples, the acellular pericardia were treated with acetic acid and collagenase. Subsequently, acellular tissues were fixed in a 0.05% genipin at 37° for 3 days. Genipin, as a crosslinking agent, was significantly less cytotoxic compared to glutaraldehyde used as a control.			
IT	55837-20-2, Halofuginone RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (biomaterial modified with composition containing angiogenic agent and crosslinker for promoting angiogenesis)			
RN	55837-20-2 HCPLUS			
CN	4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl-, rel- (9CI) (CA INDEX NAME)			

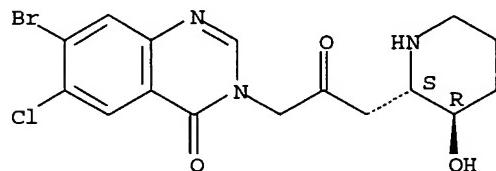
Relative stereochemistry.



L32 ANSWER 4 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:497234 HCPLUS  
DN 143:32418  
TI Medical use of reuterin  
IN Sung, Hsing-Wen; Chen, Chun-Nan; Liang, Hsiang-Fa; Tu, Hosheng  
PA Taiwan  
SO U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 282,852.  
CODEN: USXXCO  
DT Patent  
LA English  
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US2005123583	A1	20050609	2004US-0924538	20040824 <--
US2002122816	A1	20020905	2000US-0737482	20001218 <--
PRAI 2000US-0737482	A2	20001218 <--		
2002US-0282852	A2	20021029 <--		
AB Use of reuterin, a naturally occurring $\beta$ -hydroxypropinaldehyde, in the manufacture of a biocompatible implant is disclosed, which involves crosslinking an amine-containing biol. material such as chitosan, collagen, elastin, gelatin, fibrin glue, and combination thereof with reuterin.				
IT 55837-20-2, Halofuginone				
RL: DEV (Device component use); TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (medical use of reuterin-containing implants)				
RN 55837-20-2 HCPLUS				
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)				

Relative stereochemistry.



L32 ANSWER 5 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:497233 HCPLUS  
DN 143:32417  
TI Drug-eluting stent having collagen drug carrier chemically treated with genipin  
IN Sung, Hsing-Wen; Chen, Mei-Chin; Tu, Peter Y.; Tu, Hosheng  
PA Taiwan  
SO U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. Ser. No. 717,162.  
CODEN: USXXCO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US2005123582	A1	20050609	2004US-0811413	20040326 <--
WO--9819718	A1	19980514	1997WO-US20113	19971104 <--
W: CA, CN, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP---1260237	A1	20021127	2002EP-0019186	19971104 <--
R: DE, FR, GB, IT				
US---6608040	B1	20030819	2001US-0297808	20010927 <--
US---6624138	B1	20030923	2002US-0211656	20020802 <--
US2003191071	A1	20031009		
US2005163818	A1	20050728	2003US-0610391	20030630 <--
AU2004289270	A1	20050526	2004AU-0289270	20041105
CA---2545136	AA	20050526	2004CA-2545136	20041105
EP---1689322	A1	20060816	2004EP-0818654	20041105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
PRAI 1996US-030701P	P	19961105 <--		
1997WO-US20113	W	19971104 <--		
2001US-0297808	A2	20010927 <--		
2002US-0211656	A2	20020802 <--		
2003US-0610391	A2	20030630		
2003US-492874P	P	20030806		
2003US-518050P	P	20031107		

2003US-0717162	A2	20031119
2004US-547935P	P	20040226
2004US-552517P	P	20040312
1997EP-0947356	A3	19971104 <--
2002US-393565P	P	20020702 <--
2004US-565438P	P	20040426
2004US-574501P	P	20040526
2004US-0610391	A	20040630
2004US-585775P	P	20040706
2004WO-US37217	W	20041105

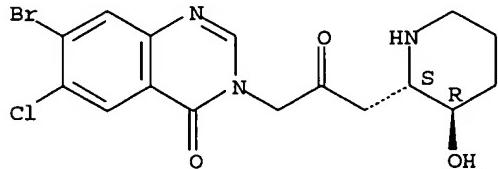
AB A method for treating vulnerable plaques of a patient, comprising:  
 providing a biodegradable stent comprising a first supporting zone made of  
 a first biodegradable material, wherein the supporting zone comprises at  
 least a portion of continuous circumference of the stent; and a second  
 therapeutic zone made of a second biodegradable material, wherein the  
 therapeutic zone comprises at least one bioactive agent; delivering the  
 biodegradable stent to the vulnerable plaques; orienting the therapeutic  
 zone at about the luminal surface of the vulnerable plaque; and releasing  
 the at least one bioactive agent for treating the vulnerable plaques.

IT 55837-20-2, Halofuginone  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (drug-eluting stent having collagen drug carrier chemical treated with  
 genipin)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-  
 piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L32 ANSWER 6 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2005:77978 HCAPLUS  
 DN 142:162660  
 TI Biodegradable stent with crosslinked bioactive agent for slow release  
 IN Sung, Hsing-Wen; Chen, Mei-Chin; Tu, Peter Y.; Tu, Hosheng  
 PA Taiwan  
 SO U.S. Pat. Appl. Publ., 45 pp., Cont.-in-part of U.S. Ser. No. 610,391.  
 CODEN: USXXCO

DT Patent

LA English

FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US2005019404	A1	20050127	2004US-0916170	20040811
	US2005163818	A1	20050728	2003US-0610391	20030630 <--
	US2006034885	A1	20060216	2004US-0929047	20040827
	AU2004289270	A1	20050526	2004AU-0289270	20041105
	CA--2545136	AA	20050526	2004CA-2545136	20041105
	EP---1689322	A1	20060816	2004EP-0818654	20041105
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
	US2005163821	A1	20050728	2005US-0906239	20050210 <--
	WO2006033686	A1	20060330	2005WO-US19930	20050608
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,				

NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,  
 SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,  
 ZA, ZM, ZW  
 RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,  
 IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF,  
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM,  
 KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG,  
 KZ, MD, RU, TJ, TM

PRAI	2003US-0610391	A2	20030630
	2003US-518050P	P	20031107
	2004US-547935P	P	20040226
	2004US-565438P	P	20040426
	2004US-574501P	P	20040526
	2004US-585775P	P	20040706
	1996US-030701P	P	19961105 <--
	1997WO-US20113	W	19971104 <--
	2001US-0297808	A2	20010927 <--
	2002US-0211656	A2	20020802 <--
	2004US-0610391	A	20040630
	2004US-0916170	A2	20040811
	2004WO-US37217	W	20041105
	2004US-0024101	A2	20041228

AB The present invention relates to a drug-loaded biodegradable stent or implant for drug slow release and methods for treating vulnerable plaques of a patient comprising a plurality of layers or zones, each layer or zone comprising its own specific biodegrdn. rate and its specific drug loading characteristics. Specifically, the layers and zones are configured and arranged, in combination, radially, circumferentially and longitudinally. The crosslinked biodegradable stent or implant comprises at least one layer or zone of biol. material, said biol. material comprising at least one bioactive agent and being crosslinked with a means for crosslinking said biol. material.

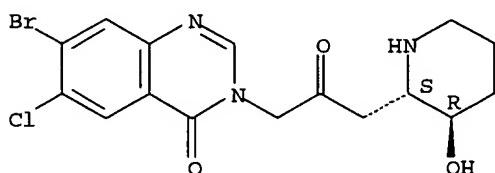
IT 55837-20-2, Halofuginone

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (biodegradable stent with crosslinked bioactive agent for slow release)

RN 55837-20-2 HCPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L32 ANSWER 7 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2004:387228 HCPLUS

DN 140:386059

TI Quinazolinone compositions for regulation of gene expression related to pathological processes

IN Pines, Mark; Nagler, Arnon; Yarkoni, Shai

PA State of Israel, Ministry of Agriculture, Israel; Hadassit Medical Research Services and Development Ltd.; Collgard Biopharmaceuticals Ltd.

SO PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO2004039308 A2 20040513 2003WO-IL00900 20031030 <--  
 WO2004039308 A3 20040708  
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,  
 CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,  
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,  
 NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,  
 TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,  
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,  
 TR, BF, BJ, CF, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 CA---2504388 AA 20040513 2003CA-2504388 20031030 <--  
 AU2003278579 A1 20040525 2003AU-0278579 20031030 <--  
 EP---1558261 A2 20050803 2003EP-0769875 20031030 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 JP2006504769 T2 20060209 2004JP-0547952 20031030 <--  
 PRAI 2002US-422487P P 20021031 <--  
 2003WO-IL00900 W 20031030

OS MARPAT 140:386059

AB The invention discloses pharmaceutical compns. for modifying gene expression in a pathol. process, thereby preventing or ameliorating the process. More particularly the compns. comprise quinazolinones, especially halofuginone, for inhibiting or preventing alterations in gene expression during fibrosis. The invention particularly relates to pharmaceutical compns. for improving the regeneration of cirrhotic liver.

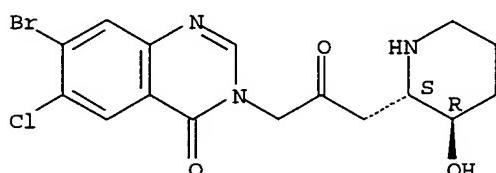
IT 55837-20-2, Halofuginone

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (Quinazolinone compns. for regulation of gene expression related to pathol. processes)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L32 ANSWER 8 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:935094 HCAPLUS

DN 140:210727

TI Compound preparation or fodder for treating parasite in fish

IN Wang, Yuwan; Pan, Zhende; Dai, Xiaoxi; Xue, Yan

PA Peop. Rep. China

SO Faming Zhanli Shenqing Gongkai Shuomingshu, 8 pp.

CODEN: CNXKEV

DT Patent

LA Chinese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN---1386507	A	20021225	2001CN-0118238	20010522 <--
PRAI	2001CN-0118238		20010522 <--		

AB The compound preparation (such as microparticle, suspension, powder, etc.) contains 0.001 - 10% macrolide parasiticide and/or other drug. The content of macrolide in 1000 kg fodder is 0.05 - 50 g. The macrolide

parasiticide is abamectin, ivermectin, emamectin or its benzoate, eprinomectin, doramectin, or moxidectin.

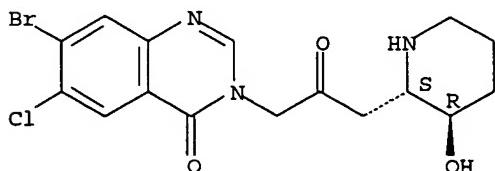
IT 55837-20-2, Halofuginone

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(compound preparation or fodder for treating parasite in fish)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L32 ANSWER 9 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:913055 HCAPLUS

DN 139:399770

TI Medical goods comprising heparin or chitosan-based hemocompatible coating  
IN Horres, Roland; Linssen, Marita Katharina; Hoffmann, Michael; Faust,  
Volker; Hoffmann, Erika; Di Biase, Donato

PA Hemotec G.m.b.H., Germany

SO PCT Int. Appl., 93 pp.

CODEN: PIXXD2

DT Patent

LA German

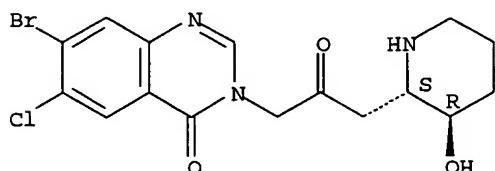
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2003094990	A1	20031120	2003WO-DE01253	20030415 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE--10221055	A1	20031127	2002DE-1021055	20020510 <--
	DE--10261986	A1	20040318	2002DE-1061986	20020510 <--
	AU2003240391	A1	20031111	2003AU-0240391	20030415 <--
	CA--2484269	AA	20031120	2003CA-2484269	20030415 <--
	CN--1543362	A	20041103	2003CN-0800770	20030415 <--
	EP--1501565	A1	20050202	2003EP-0729829	20030415 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR2003011446	A	20050315	2003BR-0011446	20030415 <--
	US2005176678	A1	20050811	2003US-0513982	20030415 <--
	CN--1665554	A	20050907	2003CN-0815926	20030415 <--
	JP2005534724	T2	20051117	2004JP-0503070	20030415 <--
	ZA2004008791	A	20050527	2004ZA-0008791	20041028 <--
	ZA2004008757	A	20050531	2004ZA-0008757	20041028 <--
PRAI	2002US-378676P	P	20020509	<--	
	2002DE-1021055	A	20020510	<--	
	2003WO-DE01253	W	20030415		
AB	The invention relates to oligo- and polysaccharides containing the sugar structural element N-acylglucosamine or N-acylgalactosamine, in addition to				

the use thereof for producing hemocompatible surfaces and to methods for coating surfaces in a hemocompatible manner with said oligo- and polysaccharides, which constitute the common biosynthetic precursor substances of heparin, heparan sulfates and chitosan. The invention also relates to methods for producing the oligo- and/or polysaccharides, in addition to diverse application options involving hemocompatible surfaces. The invention specifically relates to the use of the oligo- and/or polysaccharides on stents involving at least one hemocompatible coating that has been applied according to the invention and that contains an anti-proliferative, anti-inflammatory and/or athrombogenic active ingredient, to methods for producing said stents and to the use of the latter for preventing restenosis. Thus desulfated and reacetylated heparin was prepared; the Ac-heparin product was used for coating coronary metal stents. The stents were implanted in swines; after four weeks the animals were anesthetized and the artery segments removed for histomorphometric anal.

IT 55837-20-2, Halofuginone  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (medical goods comprising a heparin-based hemocompatible coating)  
 RN 55837-20-2 HCAPLUS  
 CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baxter Biotech Technolo Kovanen, P	1999 1999			WO---9927976 A WO---9926983 A	HCAPLUS HCAPLUS

L32 ANSWER 10 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:818303 HCAPLUS

DN 139:317470

TI Use of osteoprotegerin for the treatment and/or prevention of fibrotic disease

IN Power, Christine; Plater-Zyberk, Christine

PA Applied Research Systems ARS Holding N.V., Neth. Antilles

SO PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DT Patent

LA English

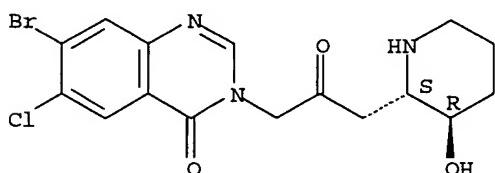
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2003084560	A2	20031016	2003WO-EP50080	20030326 <--
	WO2003084560	A3	20040205		
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	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,			

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 CA---2480084 AA 20031016 2003CA-2480084 20030326 <--  
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 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
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 JP2005530720 T2 20051013 2003JP-0581800 20030326 <--  
 ZA2004007655 A 20051102 2004ZA-0007655 20030326 <--  
 US2005143301 A1 20050630 2004US-0966845 20041015 <--  
 NO2004004658 A 20041028 2004NO-0004658 20041028 <--  
 US2006003928 A1 20060105 2005US-0510876 20050620 <--  
 PRAI 2002EP-0100364 A 20020410 <--  
 2003WO-EP50080 W 20030326

AB The invention relates to the use of osteoprotegerin for treatment and/or prevention of fibrotic diseases, in particular of scleroderma. The invention is based on the finding that administration of osteoprotegerin results in a significant amelioration of the disease in an established animal model of lung fibrosis. Lung fibrosis is one of the manifestations of scleroderma. It is therefore a first object of the invention to use osteoprotegerin for the preparation of a medicament for the treatment and/or prevention of fibrotic diseases, in particular of scleroderma. It is a second object of the invention to use a cell expressing osteoprotegerin, or an expression vector comprising the coding sequence of osteoprotegerin, for the preparation of a medicament for the treatment and/or prevention of a fibrotic disease, in particular systemic sclerosis. Pharmaceutical compns. comprising osteoprotegerin and further antifibrotic drugs, such as halofuginone, and methods of treatment comprising administering osteoprotegerin to the human body are also within the scope of the present invention.  
 IT 55837-20-2, Halofuginone  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (osteoprotegerin treatment of fibrotic diseases)  
 RN 55837-20-2 HCAPLUS  
 CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L32 ANSWER 11 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:341129 HCAPLUS  
 DN 139:333043  
 TI Effect of halofuginone on the development of tight skin (TSK) syndrome  
 AU McGaha, Tracy; Kodera, Takao; Phelps, Robert; Spiera, Harry; Pines, Mark;  
 Bona, Constantin  
 CS Department of Microbiology, The Mount Sinai School of Medicine, New York,  
 NY, 10029, USA  
 SO Autoimmunity (2002), 35(4), 277-282  
 CODEN: AUIMEI; ISSN: 0891-6934  
 PB Taylor & Francis Ltd.  
 DT Journal  
 LA English  
 AB The end point of pathogenic events in scleroderma is fibrosis of the skin and internal organs. Fibrosis in scleroderma results from the

over-synthesis and deposition of collagen in the connective tissue. The morbidity and mortality of the scleroderma is very high and presently there is no specific treatment. Halofuginone is a drug with great potential for the treatment of scleroderma since it inhibits the synthesis of collagen type I by fibroblasts. We have studied the in vivo effect of halofuginone in tight skin (TSK) mice that spontaneously develop a scleroderma-like disease due to a genetic defect. Our results demonstrate that halofuginone prevented the occurrence of skin sclerosis when administered to newborn mice and reduced cutaneous hyperplasia when administered in adult TSK mice. These effects correlated with a decreased number of cells synthesizing collagen gene transcripts and a reduction in the level of autoantibodies specific for human target antigens. These results indicate that halofuginone may have use as a therapeutic in the treatment of fibrotic disease.

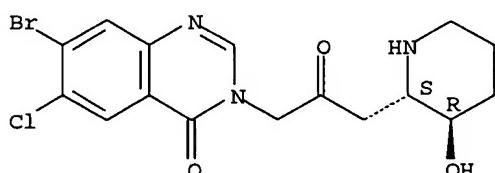
IT 55837-20-2, Halofuginone

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(effect of halofuginone on the development of tight skin (TSK) syndrome, an animal model for scleroderma)

RN 55837-20-2 HCPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bona, C	2000		677	Autoantigens and Aut	
Bona, C	1999	1	194	Curr Dir Autoimmun	HCPLUS
Bona, C	1994	6	931	Curr Opin Immunol	HCPLUS
Bruck, R	2001	33	379	Hepatology	HCPLUS
Casas, J	1987	46	763	Ann Rheum Dis	MEDLINE
Casciola-Rosen, L	1997	185	71	J Exp Med	HCPLUS
Gayraud, B	2000	150	667	J Cell Biol	HCPLUS
Granot, I	1993	1156	107	Biochem Biophys Acta	HCPLUS
Green, M	1976	82	493	Am J Pathol	MEDLINE
Hatakeyama, A	1996	167	135	Cell Immunol	HCPLUS
Keiser, H	1967	4	593	Clin Pharmacol Ther	
Kodera, T	2002	99	3800	Proc Natl Acad Sci U	HCPLUS
Levy-Schaffer, F	1996	106	84	J Investig Dermatol	
McGaha, T	2001	116	136	J Investig Dermatol	HCPLUS
McGaha, T	2002	118	461	J Investig Dermatol	HCPLUS
Murai, C	1998	28	151	Autoimmunity	
Muryoi, T	1992	143	43	Cell Immunol	HCPLUS
Muryoi, T	1992	175	1109	J Exp Med	
Nagler, A	1999	80	558	Am J Obstet Gynecol	
Nagler, A	1996	154	1082	Am J Respir Crit Care	MEDLINE
Nagler, A	1999	68	1806	Transplantation	HCPLUS
Nimni, M	1968	243	1457	J Biol Chem	HCPLUS
Nyska, M	1996	34	97	Connect Tiss Res	HCPLUS
Pines, M	1997	27	391	J Hepatol	HCPLUS
Rossi, G	1984	129	850	Am Rev Respir Dis	MEDLINE
Saito, S	2000	6	1942	Mol Med	
Sakai, L	1996	103	2499	J Cell Biol	
Seibold, J	2000	132	871	Ann Intern Med	HCPLUS

Shibata, S	1993	92	984	J Clin Investig	HCAPLUS
Siracusa, L	1996	6	300	Genome Res	HCAPLUS
Stratton, R	2001	108	241	J Clin Investig	HCAPLUS
Varga, J	1995	12	187	Intern Rev Immunol	MEDLINE
Wallis, D	2001	44	1855	Arthritis Rheum	HCAPLUS

L32 ANSWER 12 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:176833 HCAPLUS

DN 139:255042

TI Inhibition of anastomotic intimal hyperplasia by a synthetic nonsulphated heparin-mimicking compound

AU Shargal, Yaron; Viola, Nicola; Nagler, Arnon; Merin, Gideon; Schmidt, Annette; Buddecke, Erick; Ben-Sasson, Shmuel A.; Vlodavsky, Israel

CS Department of Thoracic and Cardiovascular Surgery, Hadassah-University Hospital, Jerusalem, Israel

SO Experimental & Clinical Cardiology (2002), 7(2/3), 73-79  
CODEN: ECCAF7; ISSN: 1205-6626

PB Pulsus Group Inc.

DT Journal

LA English

AB Despite extensive research in the design of endovascular catheters and advanced surgical techniques, stenosis recurs in a large percentage of patients undergoing angioplasty or anastomosis. Hence, neointimal hyperplasia, caused by migration and proliferation of vascular smooth muscle cells (SMC), remains a significant limitation to the relief of obstructive-occlusive vascular disease. It has been previously demonstrated that heparin displaces active basic fibroblast growth factor (bFGF) from the luminal surface of blood vessels. Sequestration of the displaced bFGF by injured areas of the vessel wall is inhibited in the presence of a synthetic nonsulfated heparin-mimicking polyanionic compound (RG-13577). This compound also induces a phenotype transformation of coronary SMC into a metabolically active hypertrophic status that could promote repair processes after balloon angioplasty while inhibiting cell proliferation. In this paper, the result of a continuous administration of compound RG-13577 both in the rat carotid catheter injury model and in a newly developed rat model of surgical arterial vascular injury (anastomosis) is reported: it causes a profound inhibition of intimal hyperplasia in both models. A combined treatment with heparin/heparan sulfate mimetics and halofuginone, a potent inhibitor of collagen synthesis, extracellular matrix deposition and SMC proliferation, is expected to inhibit restenosis through inhibition of both signals/activities induced by soluble mols. (ie, heparin-binding growth factors) and components of the extracellular matrix (ie, type I collagen).

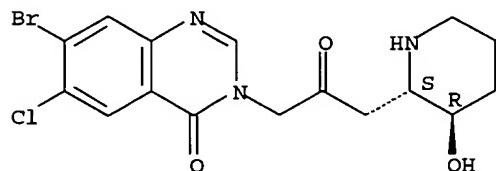
IT 55837-20-2, Halofuginone

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(nonsulfated heparin mimetic inhibits anastomotic intimal hyperplasia)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



#### RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Bar-Shavit, R	1990	1	453	Cell Regul	HCAPLUS
Benezra, M	1994	14	1992	Arterioscler Thromb	HCAPLUS
Benezra, M	2001	81	114	J Cell Biochem	HCAPLUS
Casscells, W	1992	86	723	Circulation	HCAPLUS
Castellot, J	1986	102	1979	J Cell Biol	HCAPLUS
Choi, E	1995	130	257	Arch Surg	MEDLINE
Clowes, A	1977	265	625	Nature	HCAPLUS
Ferns, G	1991	253	1129	Science	HCAPLUS
Fuster, V	1992	326	242	N Engl J Med	MEDLINE
Granot, I	1993	1156	107	Biochim Biophys Acta	HCAPLUS
Jawien, A	1992	89	507	J Clin Invest	HCAPLUS
Katz, A	1997	8	1688	J Am Soc Nephrol	HCAPLUS
Lever, R	2002	1	140	Nat Rev Drug Discov	HCAPLUS
Lindner, V	1991	68	106	Circ Res	HCAPLUS
Lindner, V	1991	88	3739	Proc Natl Acad Sci U S A	HCAPLUS
Loppnow, H	1990	85	731	J Clin Invest	HCAPLUS
Medalion, B	1997	95	1853	Circulation	HCAPLUS
Miao, H	1997	99	1565	J Clin Invest	HCAPLUS
Nagler, A	1997	17	194	Arterioscler Thromb	HCAPLUS
Neuger, L	2001	157	13	Atherosclerosis	HCAPLUS
Raman, V	1998	3	133	Semin Interv Cardiol	MEDLINE
Regan, J	1993	8	317	J Bioact Compat Poly	HCAPLUS
Rochnik, E	1998	101	1889	J Clin Invest	HCAPLUS
Ross, R	1993	362	801	Nature	HCAPLUS
Schmidt, A	1999	147	387	Atherosclerosis	HCAPLUS
Schmidt, A	1995	67	130	Eur J Cell Biol	HCAPLUS
Schmidt, A	1992	267	19242	J Biol Chem	HCAPLUS
Spivak-Krouzman, T	1994	79	1015	Cell	
Vlodavsky, I	1996	15	177	Cancer Metastasis Rev	HCAPLUS
Vlodavsky, I	1999	5	793	Nat Med	HCAPLUS

L32 ANSWER 13 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:881170 HCAPLUS

DN 139:47044

TI Halofuginone inhibition of COL1A2 promoter activity via a c-Jun-dependent mechanism

AU McGaha, Tracy L.; Kodera, Takao; Spiera, Harry; Stan, Alexandru C.; Pines, Mark; Bona, Constantin A.

CS The Mount Sinai School of Medicine, New York, NY, USA

SO Arthritis &amp; Rheumatism (2002), 46(10), 2748-2761

CODEN: ARHEAW; ISSN: 0004-3591

PB John Wiley &amp; Sons, Inc.

DT Journal

LA English

AB The naturally occurring compound halofuginone has been shown to antagonize collagen synthesis by fibroblasts both in vitro and in vivo. We previously demonstrated that this inhibitory property was related to the ability of halofuginone to disrupt transforming growth factor  $\beta$  signal transduction. The present study further analyzed the ability of halofuginone to affect transcription factors that can regulate type I collagen gene expression by examining its effect on c-Jun, the neg. regulator of collagen gene transcription. The phosphorylation state of c-Jun in the presence of halofuginone was examined via direct Western blotting, and the transcriptional activity of the activator protein 1 (AP-1) binding element via electrophoretic mobility shift assay and luciferase reporter assay. We determined whether the effect of halofuginone on collagen synthesis was dependent on the presence of c-Jun by ectopic expression of a wild-type or dominant-neg. c-Jun construct in the presence of halofuginone and assaying  $\alpha 2(I)$  collagen promoter strength via luciferase reporter assay. The effect of halofuginone on  $\alpha 2(I)$  collagen message levels in fibroblasts when wild-type or dominant-neg. c-Jun was overexpressed was determined. We also determined whether halofuginone had an effect on the phosphorylation state of c-Jun in the skin of TSK/+ mice via immunohistochem. Treatment of fibroblasts with 10-8M halofuginone enhanced basal and mitogen-mediated phosphorylation of c-Jun in culture. This elevated phosphorylation of c-Jun correlated with enhanced DNA

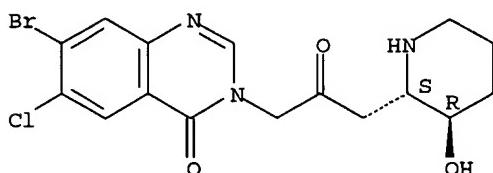
binding and transcriptional activation of an AP-1 complex consisting of c-Jun and Fos but lacking the c-Jun antagonist JunB. Overexpression of c-Jun enhanced in a dose-dependent manner the ability of halofuginone to inhibit the activity of a luciferase reporter construct under control of the -3200-bp to +54-bp COL1A2 promoter, whereas the expression of a dominant-neg. c-Jun construct abolished this effect. Northern blotting showed that overexpression of c-Jun enhanced the ability of halofuginone to reduce collagen  $\alpha_2$ (I) mRNA levels in fibroblasts, whereas expression of the dominant-neg. c-Jun abolished this effect. Topical administration of a halofuginone-containing cream for 20 days to TSK mice, which spontaneously develop dermal fibrosis, greatly increased the phosphorylated form of c-Jun in the skin; this was followed by a decrease in skin thickness and type I collagen mRNA expression. Our findings illustrate the powerful down-regulatory property of c-Jun toward type I collagen and establish that halofuginone exerts its effect on collagen synthesis in a c-Jun-dependent manner.

IT 55837-20-2, Halofuginone  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (halofuginone inhibition of COL1A2 promoter activity via c-Jun-dependent mechanism)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anderson, M	1984	31	391	Biol Reprod	MEDLINE
Bona, C	2000	18	119	Clin Rev Allergy Imm	HCAPLUS
Brown, P	1994	9	791	Oncogene	HCAPLUS
Bruck, R	2001	33	379	Hepatology	HCAPLUS
Chen, S	2000	183	381	J Cell Physiol	HCAPLUS
Chen, S	1999	112	49	J Invest Dermatol	HCAPLUS
Chinenov, Y	2001	20	2438	Oncogene	MEDLINE
Chung, K	1996	271	3272	J Biol Chem	HCAPLUS
Dennler, S	2000	275	28858	J Biol Chem	HCAPLUS
Eickelberg, O	2001	15	797	FASEB J	HCAPLUS
Elkin, M	1999	59	4111	Cancer Res	HCAPLUS
Elkin, M	2000	14	2477	FASEB J	HCAPLUS
Fang, C	2000	57	2626	Kidney Int	HCAPLUS
Fisher, G	1998	101	1432	J Clin Invest	HCAPLUS
Fisher, G	2000	106	663	J Clin Invest	HCAPLUS
Funk, W	1992	12	2866	Mol Cell Biol	HCAPLUS
Gharaee-Kermani, M	2001	15	138	Cytokine	HCAPLUS
Granot, I	1993	1156	107	Biochem Biophys Acta	HCAPLUS
Granot, I	1991	70	1559	Poult Sci	
Greenwel, P	1997	272	19738	J Biol Chem	HCAPLUS
Hai, T	1991	88	3270	Proc Natl Acad Sci U	
Halevy, O	1996	52	1057	Biochem Pharmacol	HCAPLUS
Holmes, A	2001	276	10594	J Biol Chem	HCAPLUS
Ihn, H	2000	43	2240	Arthritis Rheum	HCAPLUS
Ihn, H	1997	272	24666	J Biol Chem	HCAPLUS
Kawakami, T	1998	110	47	J Invest Dermatol	HCAPLUS

Kovary, K	1992	12	5015	Mol Cell Biol	HCAPLUS
Lallemand, D	1997	14	819	Oncogene	HCAPLUS
Landschulz, W	1988	240	1759	Science	HCAPLUS
Lee, C	2001	194	809	J Exp Med	HCAPLUS
Lee, H	1998	30	2495	J Mol Cell Cardiol	HCAPLUS
Levy, M	2000	32	218	Hepatology	HCAPLUS
Martin, P	1997	276	75	Science	HCAPLUS
McCormick, L	1999	163	5693	J Immunol	HCAPLUS
McGaha, T	2002	118	461	J Invest Dermatol	HCAPLUS
McHugh, N	1988	47	43	Ann Rheum Dis	MEDLINE
Mueller, R	1999	184	1093	J Exp Med	
Nagler, A	1999	180	558	Am J Obstet Gynecol	HCAPLUS
Philips, N	1995	270	9313	J Biol Chem	HCAPLUS
Piccinni, M	1999	29	2241	Eur J Immunol	HCAPLUS
Pines, M	2001	62	1221	Biochem Pharmacol	HCAPLUS
Romanelli, R	1997	122	1047	Br J Pharmacol	HCAPLUS
Saed, G	1998	134	963	Arch Dermatol	HCAPLUS
Sakai, L	1996	103	2499	J Cell Biol	
Salmon-Ehr, V	1996	132	802	Arch Dermatol	MEDLINE
Sato, S	2000	27	149	J Rheumatol	HCAPLUS
Seibold, J	1997	25	302	J Rheumatol	
Serpier, H	1997	109	158	J Invest Dermatol	HCAPLUS
Silbiger, S	1999	55	1268	Kidney Int	HCAPLUS
Siracusa, L	1996	6	300	Genomic Res	HCAPLUS
Skuballa, W	1985		17	Prostacyclin and its	
Slack, J	1995	58	380	J Cell Biochem	HCAPLUS
Steen, V	1998	17	48	Semin Cutan Med Surg	MEDLINE
Stratton, R	2001	108	241	J Clin Invest	HCAPLUS
Szabowski, A	2000	103	745	Cell	HCAPLUS
Underwood, D	2000	279	L895	Am J Physiol Lung Ce	HCAPLUS
Unemori, E	1992	99	337	J Invest Dermatol	HCAPLUS
Vaupel, M	1985	33	303	J Histochem Cytochem	HCAPLUS
Vergeer, W	2000	377	69	Arch Biochem Biophys	HCAPLUS
Verrecchia, F	2001	20	2205	Oncogene	HCAPLUS
Zhang, W	2000	275	39237	J Biol Chem	HCAPLUS
Zhang, Y	1998	394	909	Nature	HCAPLUS

L32 ANSWER 14 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:846333 HCAPLUS

DN 138:3859

TI Halofuginone contamination in feeds as a cause of residues in eggs

AU Yakkundi, S.; Cannavan, A.; Young, P. B.; Elliott, C. T.; Kennedy, D. G.

CS Department of Veterinary Science, Queen's University, Belfast, UK

SO Analytica Chimica Acta (2002), 473(1-2), 177-182

CODEN: ACACAM; ISSN: 0003-2670

PB Elsevier Science B.V.

DT Journal

LA English

AB An experiment was designed to establish the relationship between halofuginone (HFG) contaminated feed and HFG residues in eggs. Five groups of six-layer hens each were fed with HFG contaminated diets at concns. ranging between 1 and 10% of the therapeutic dose for broilers (3 mg kg<sup>-1</sup>) for 14 days. The group fed on the highest dose was then fed with a HFG-free diet for a further 14 days. Eggs were collected, homogenized, extracted and analyzed using a method employing liquid chromatog. (LC) coupled to electrospray (ES)-tandem mass spectrometry (MS-MS). In general, the HFG concentration was much lower than those seen in similar studies on nicarbazin. However, comparison of the HFG concns. measured in eggs and the maximum residue limit (MRL) for HFG in bovine muscle suggested that feed contamination could give rise to potentially significant HFG residues in eggs. Depletion of HFG from eggs, following the feeding of an HFG-free diet was 2.6 days, somewhat slower than the corresponding values for lasalocid and nicarbazin (1.1 and 1.6 days, resp.).

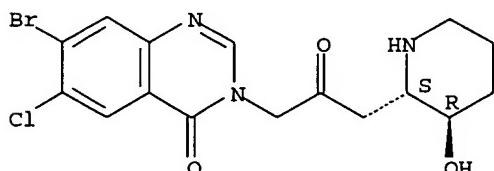
IT 55837-20-2, Halofuginone

RL: POL (Pollutant); OCCU (Occurrence)

(halofuginone in eggs caused by chicken feed contamination)

RN 55837-20-2 HCAPLUS  
 CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Analytical Methods Comm	1984	109	171	Analyst	HCAPLUS
Andre, F	2001	20	435	Trends Anal Chem	HCAPLUS
Cannavan, A	2000	17	829	Food Addit Contam	HCAPLUS
De Brabander, H	2000		248	Proceedings of the C	
Kennedy, D	1998	123	2529	Analyst	MEDLINE
Kennedy, D	1996	13	787	Food Addit Contam	HCAPLUS
Kennedy, D	1998	15	535	Food Addit Contam	HCAPLUS
Kennedy, D	2000	882	37	J Chromatogr B	HCAPLUS
McEvoy, J				Food Addit Contam, a	
The European Agency for	2000				
Yakkundi, S				J Chromatogr B, acce	
Young, R	2001			Soil association rep	
Zimmermann, N	1994	73	326	Poultry Sci	HCAPLUS

L32 ANSWER 15 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:600553 HCAPLUS

DN 138:379131

TI Halofuginone, a collagen type I inhibitor improves liver regeneration in cirrhotic rats

AU Spira, Gadi; Mawasi, Nidal; Paizi, Melia; Anbinder, Natali; Genina, Olga; Alexiev, Rosaly; Pines, Mark

CS Rappaport Family Institute for Research in the Medical Sciences, The Bruce Rappaport Faculty of Medicine, Department of Anatomy and Cell Biology, Technion, Haifa, Israel

SO Journal of Hepatology (2002), 37(3), 331-339

CODEN: JOHEEC; ISSN: 0168-8278

PB Elsevier Science Ltd.

DT Journal

LA English

AB Hepatic fibrosis involves excess deposition of extracellular connective tissue of which collagen type I fibers form the predominant component. Left untreated it develops into cirrhosis, often linked with hepatocellular carcinoma. Owing to the fact that cirrhotic liver regeneration is impaired, resection of hepatocellular carcinoma associated with cirrhosis is questionable. The aim of the present study was to determine the potential of halofuginone, a collagen type I inhibitor, in improving liver regeneration in cirrhotic rats. Partial hepatectomy (70%) was performed in thioacetamide-induced cirrhotic rats fed a halofuginone-containing diet. Liver regeneration was monitored by mass and proliferating cell nuclear antigen. The Ishak staging system and hydroxyproline content were used to evaluate the level of fibrosis. Halofuginone administered prior to and following partial hepatectomy did not inhibit normal liver regeneration despite the reduced levels of collagen type I mRNA. When given to rats with established fibrosis, it caused a significant reduction in  $\alpha$  smooth muscle actin, TIMP-2, collagen type I gene expression and collagen deposition. Such animals demonstrated improved capacity for regeneration. Thus, halofuginone may

prove useful in improving survival of patients with hepatocellular carcinoma and cirrhosis undergoing surgical resection.

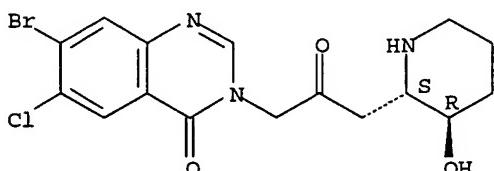
IT 55837-20-2, Halofuginone

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(halofuginone, a collagen type I inhibitor, improves liver regeneration in cirrhotic rats)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abramovitch, R	1999	1	321	Neoplasia	HCAPLUS
Alcolado, R	1997	92	103	Clin Sci (Colch)	HCAPLUS
Assy, N	1999	30	911	J Hepatol	HCAPLUS
Aycock, R	1989	23	19	Connect Tissue Res	MEDLINE
Bruck, R	2001	33	379	Hepatology	HCAPLUS
Burt, A	1993	170	105	J Pathol	MEDLINE
Choi, E	1995	130	257	Arch Surg	MEDLINE
Geisler, S	1997	289	173	Cell Tissue Res	HCAPLUS
Halevy, O	1996	52	1057	Biochem Pharmacol	HCAPLUS
Hernandez-Munoz, R	2001	34	677	Hepatology	MEDLINE
Higgins, G	1931	12	186	Arch Pathol	
Iredale, J	1997	29	43	Int J Biochem Cell B	HCAPLUS
Iredale, J	1992	90	282	J Clin Invest	HCAPLUS
Ishak, K	1995	22	696	J Hepatol	MEDLINE
Jamall, I	1981	112	70	Anal Biochem	HCAPLUS
Jonsson, J	2001	121	148	Gastroenterology	HCAPLUS
Junquiera, L	1979	94	96	Anal Biochem	MEDLINE
Kaibori, M	1997	27	381	J Hepatol	HCAPLUS
Kaido, T	1998	74	173	J Surg Res	HCAPLUS
Kim, T	2000	31	75	Hepatology	HCAPLUS
Kraizer, J	2001	287	209	Biochem Biophys Res	
Levi-Schaffer, F	1996	106	84	J Invest Dermatol	HCAPLUS
Li, D	1999	14	618	J Gastroenterol Hepa	MEDLINE
Martinez-Hernandez, A	1995	9	1401	FASEB J	HCAPLUS
Masson, S	2000	5	173	Apoptosis	HCAPLUS
Mavier, P	1995	22	111	J Hepatol	MEDLINE
McGaha, T	2002	118	461	J Invest Dermatol	HCAPLUS
Milani, S	1994	144	528	Am J Pathol	HCAPLUS
Monto, A	2001	28	441	Semin Oncol	MEDLINE
Murawaki, Y	1997	26	1213	J Hepatol	MEDLINE
Nagasue, N	1987	206	30	Ann Surg	MEDLINE
Nagler, A	1999	180	558	Am J Obstet Gynecol	MEDLINE
Nagler, A	1996	154	1082	Am J Respir Crit Car	MEDLINE
Nagler, A	1998	227	575	Ann Surg	MEDLINE
Nagler, A	1999	68	1806	Transplantation	HCAPLUS
Nakamura, T	2000	32	247	Hepatology	HCAPLUS
Nyska, M	1996	34	97	Connect Tissue Res	HCAPLUS
Ogura, Y	2001	48	545	Hepatogastroenterolo	HCAPLUS
Panduro, A	1988	8	259	Hepatology	HCAPLUS
Pines, M	2001	62	1221	Biochem Pharmacol	HCAPLUS

Pines, M	1998	30	445	Gen Pharmacol	HCAPLUS
Pines, M	1997	27	391	J Hepatol	HCAPLUS
Qi, Z	1999	96	2345	Proc Natl Acad Sci U S A	HCAPLUS
Ramadori, G	1992	103	1313	Gastroenterology	HCAPLUS
Rosser, J	1995	129	1421	J Cell Biol	HCAPLUS
Schuppan, D	1990	10	1	Semin Liver Dis	MEDLINE
Ueki, T	1999	5	226	Nat Med	HCAPLUS
Yamamoto, H	1995	21	155	Hepatology	HCAPLUS

L32 ANSWER 16 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:584274 HCAPLUS

DN 137:325539

TI Re-revision of the stereo structure of piperidine lactone, an intermediate in the synthesis of febrifugine

AU Takeuchi, Yasuo; Azuma, Kumiko; Abe, Hitoshi; Sasaki, Kenji; Harayama, Takashi

CS Faculty of Pharmaceutical Sciences, Okayama University, Okayama, 700-8530, Japan

SO Chemical & Pharmaceutical Bulletin (2002), 50(7), 1011-1012  
CODEN: CPBTAL; ISSN: 0009-2363

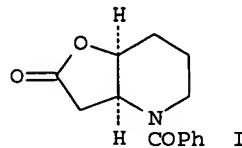
PB Pharmaceutical Society of Japan

DT Journal

LA English

OS CASREACT 137:325539

GI



AB The stereo structure of piperidine lactone I, an intermediate of the antimalarial agent febrifugine prepared by a synthetic method, was re-revised to the cis-form from the trans form.

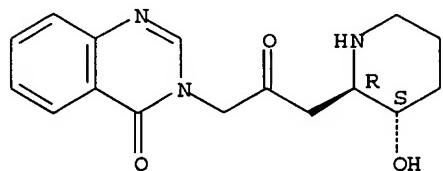
IT 24159-07-7P, Febrifugine

RL: PNU (Preparation, unclassified); PREP (Preparation)  
(revision of stereo structure of piperidine lactone, an intermediate in synthesis of febrifugine)

RN 24159-07-7 HCAPLUS

CN 4(3H)-Quinazolinone, 3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ablondi, E	1952	17	14	J Org Chem	
Baker, B	1952	17	132	J Org Chem	HCAPLUS
Baker, B	1953	18	153	J Org Chem	HCAPLUS
Baker, B	1953	18	178	J Org Chem	HCAPLUS

Baker, B	1955	20	136	J Org Chem	HCAPLUS
Barringer, D	1973	38	1937	J Org Chem	HCAPLUS
Burgess, L	1996	37	3255	Tetrahedron Lett	HCAPLUS
Hill, R		1962	858	Chem Ind	
Hutchings, B	1952	17	19	J Org Chem	HCAPLUS
Kobayashi, S	1999	64	6833	J Org Chem	HCAPLUS
Kobayashi, S	1999	40	2175	Tetrahedron Lett	HCAPLUS
Koepfli, J	1947	69	1837	J Am Chem Soc	HCAPLUS
Koepfli, J	1947	69	1837	J Am Chem Soc	HCAPLUS
Koepfli, J	1949	71	1048	J Am Chem Soc	HCAPLUS
Murata, K	1998	61	729	J Nat Prod	HCAPLUS
Okitsu, O	2001	66	809	J Org Chem	HCAPLUS
Okitsu, O		2000	989	Synlett	
Ooi, H	2001	3	953	Org Lett	HCAPLUS
Sugiura, M	2001	3	477	Org Lett	HCAPLUS
Sugiura, M		2001	1225	Synlett	
Takaya, Y	1999	42	3163	J Med Chem	HCAPLUS
Takeuchi, Y		2000	1643	Chem Commun	
Takeuchi, Y	1999	47	905	Chem Pharm Bull	HCAPLUS
Takeuchi, Y	2001	49	721	Chem Pharm Bull	HCAPLUS
Takeuchi, Y	1999	51	1869	Heterocycles	HCAPLUS
Takeuchi, Y		1999	1814	Synthesis	
Takeuchi, Y	2001	57	1213	Tetrahedron	HCAPLUS
Taniguchi, T	2000	2	3193	Org Lett	HCAPLUS

L32 ANSWER 17 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:561803 HCAPLUS

DN 138:198395

TI Halofuginone does not reduce fibrosis in bleomycin-induced lung injury

AU Tzurel, Anat; Segel, Michael J.; Or, Reuven; Goldstein, Ronald H.; Breuer, Raphael

CS Lung Cellular and Molecular Biology Laboratory-Institute of Pulmonology, Hadassah University Hospital and the Hebrew University-Hadassah Medical School, Jerusalem, Israel

SO Life Sciences (2002), 71(14), 1599-1606

CODEN: LIFSAK; ISSN: 0024-3205

PB Elsevier Science Inc.

DT Journal

LA English

AB Halofuginone, a coccidiostatic alkaloid, has anti-fibrotic properties, and may be useful as a therapeutic agent in lung fibrosis. To test this hypothesis we investigated the effect of halofuginone on bleomycin-induced lung fibrosis in Sprague-Dawley rats. Treatment groups included: (1) a single intratracheal (IT) instillation of 1.2U bleomycin, and i.p. (IP) injection of halofuginone (0.5 mg/dose), every other day; (2) IT 1.2U bleomycin and IP distilled water (D.W.), every other day; (3) IT 0.8U bleomycin and daily IP halofuginone (0.5 mg/dose); (4) IT 0.8U bleomycin and daily IP D.W.; (5) IT saline and IP halofuginone, every other day; (6) IT saline and daily IP D.W.; (7) IT 0.625U bleomycin and oral halofuginone (10 mg/kg rodent lab chow); (8) IT 0.625U bleomycin and standard lab chow. Animals were studied 14 days after IT instillation. Lung injury was evaluated by total and differential cell count in bronchoalveolar lavage fluid, by a semi-quant. morphol. index of lung injury, and by biochem. anal. of lung hydroxyproline content. Overt signs of lung injury were apparent in bleomycin-treated rats by all measures. These changes were not affected by treatment with halofuginone, irresp. of the treatment regimen used. This study does not support the use of halofuginone to prevent or ameliorate lung fibrosis.

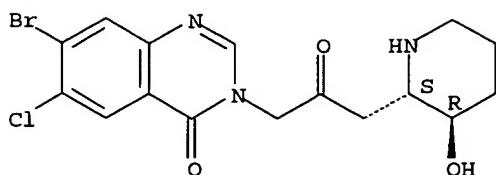
IT 55837-20-2, Halofuginone

RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (halofuginone does not reduce fibrosis in bleomycin-induced lung injury)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Berkman, N	2001	68	169	Respiration	HCAPLUS
Fine, A	1990	24	237	Connect Tissue Res	MEDLINE
Genovese, C	1984	23	6210	Biochemistry	HCAPLUS
Giri, S	1980	33	1	Exp Mol Pathol	HCAPLUS
Giri, S	1993	48	959	Thorax	MEDLINE
Goldstein, R	1986	11	245	Exp Lung Res	HCAPLUS
Katzenstein, A	1998	157	1301	Am J Respir Crit Care Med	MEDLINE
Kremer, S	1999	66	455	Respiration	HCAPLUS
Laxer, U	1999	25	531	Exp Lung Res	HCAPLUS
Lossos, I	2000	67	2873	Life Sci	HCAPLUS
Nagler, A	1996	154	1082	Am J Respir Crit Care Med	MEDLINE
Pines, M	1998	30	445	Gen Pharmacol	HCAPLUS
Raghow, B	1989	84	1836	J Clin Invest	MEDLINE
Segel, M	2001	14	403	Pulm Pharmacol Ther	HCAPLUS
Snedecor, G	1967		258	Statistical Methods	
Snider, G	1978	117	1099	Am Rev Respir Dis	HCAPLUS
Snider, G	1978	117	289	Am Rev Respir Dis	HCAPLUS
Sulavik, S	1995	80	1	Pulmonary Fibrosis L	

L32 ANSWER 18 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:533022 HCAPLUS

DN 137:295118

TI Synthesis and antimalarial activity of febrifugine

AU Takeuchi, Yasou; Harayama, Takashi

CS Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka, Okayama, 700-8530, Japan

SO Trends in Heterocyclic Chemistry (2001), 7, 65-74

CODEN: THCCE6

PB Research Trends

DT Journal; General Review

LA English

AB A review. (+)-Febrifugine (I), which was isolated in 1947 from *Dichroa febrifuga* and *Hydrangea umbellata* along with isofebrifugine, is a well-known candidate antimalarial agent. Repeated errors and corrections in determining its structure have caused much confusion in the study of the relationship between the structure and antimalarial activity of febrifugine derivs. Recently, it was reported that , had higher activity than antimalarial drugs in clin. use and a derivative more potent than I was found. Details of the history and synthesis of I were described in this review.

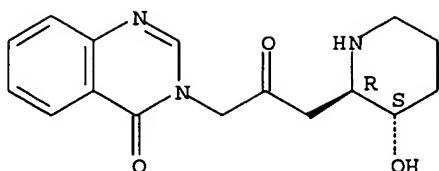
IT 24159-07-7P, (+)-Febrifugine

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(synthesis and antimalarial activity of febrifugine)

RN 24159-07-7 HCAPLUS

CN 4(3H)-Quinazolinone, 3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ablondi, F	1952	17	14	J Org Chem	HCAPLUS
Baker, B	1952	17	116	J Org Chem	HCAPLUS
Baker, B	1952	17	132	J Org Chem	HCAPLUS
Baker, B	1952	17	141	J Org Chem	HCAPLUS
Baker, B	1952	17	52	J Org Chem	HCAPLUS
Baker, B	1952	17	68	J Org Chem	HCAPLUS
Baker, B	1952	17	77	J Org Chem	HCAPLUS
Baker, B	1952	17	97	J Org Chem	HCAPLUS
Baker, B	1953	18	133	J Org Chem	HCAPLUS
Baker, B	1953	18	153	J Org Chem	HCAPLUS
Baker, B	1953	18	178	J Org Chem	HCAPLUS
Baker, B	1955	20	136	J Org Chem	HCAPLUS
Barringer, D	1973	38	1933	J Org Chem	HCAPLUS
Barringer, D	1973	38	1937	J Org Chem	HCAPLUS
Burgess, L	1996	37	3255	Tetrahedron Lett	HCAPLUS
Chien, P	1970	13	867	J Med Chem	HCAPLUS
Fishman, M	1970	13	155	J Med Chem	HCAPLUS
Hewitt, R	1952	1	768	J Trop Med Hyg	HCAPLUS
Hill, R	1962		858	Chem Ind	HCAPLUS
Kobayashi, S	1999	64	6833	J Org Chem	HCAPLUS
Kobayashi, S	1999	40	2175	Tetrahedron Lett	HCAPLUS
Koepfli, J	1947	69	1837	J Am Chem Soc —	HCAPLUS
Koepfli, J	1949	71	1048	J Am Chem Soc	HCAPLUS
Koepfli, J	1950	72	3323	J Am Chem Soc	HCAPLUS
Ohi, H	2000			The 120th Annual Mee	
Takaya, Y	1999	42	3163	J Med Chem	HCAPLUS
Takeuchi, Y	2000		1643	Chem Commun	HCAPLUS
Takeuchi, Y	1999	47	905	Chem Pharm Bull	HCAPLUS
Takeuchi, Y	1999		1814	Synthesis	HCAPLUS
Takeuchi, Y	2001			Tetrahedron in press	
Takeuchi, Y				unpublished data	
Taniguchi, T	2000	2	3193	Org Lett	HCAPLUS
Uesato, S	1998	46	1	Chem Pharm Bull	HCAPLUS

L32 ANSWER 19 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:531106 HCAPLUS

DN 137:368801

TI Immunoassay and HPLC detection of halofuginone in chicken liver samples obtained from commercial slaughterhouses: a combined study

AU Beier, Ross C.; Feldman, Steve F.; Dutko, Terry J.; Petersen, H. Delvar; Stanker, Larry H.

CS Southern Plains Agricultural Research Center, Agricultural Research Service, College Station, TX, 77845-4988, USA

SO Food and Agricultural Immunology (2002), 14(1), 29-40  
CODEN: FAIMEZ; ISSN: 0954-0105

PB Carfax Publishing

DT Journal

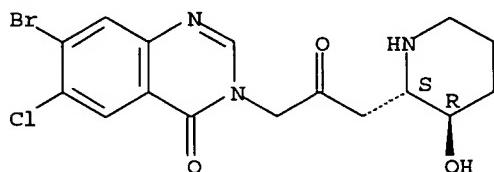
LA English

AB Halofuginone (Hal) is a feed additive used worldwide to prevent coccidiosis in com. poultry production. The current regulatory method for determining the action level of Hal residues in poultry involves measuring parent Hal in liver tissue by HPLC. A competitive ELISA (cELISA) for Hal

was evaluated with respect to HPLC in determining Hal in 473 samples of chicken liver tissue obtained from com. poultry slaughterhouses. Chicken liver samples were divided, and analyzed by both the US Department of Agriculture, Food Safety and Inspection Service's (FSIS's) regulatory method, and by the US Department of Agriculture, Agricultural Research Service's (ARS's) cELISA method described here. The lower level of detection for Hal was 50 ppb by the FSIS HPLC method and 38 ppb by the ARS cELISA method. The lower cutoff limit for this study was 50 ppb as mandated by FSIS SOP. There was good agreement in the results obtained by HPLC and cELISA. In addition, the cELISA method does not require the use of organic solvents. These data clearly demonstrate that the cELISA method could be used as a screening method for the anal. of Hal in chicken liver tissue. If the cELISA had been used as a screening tool in this study, then only 6 samples ( $\geq$  100 and < 160 ppb) out of the 473 samples analyzed would have required further anal. by HPLC. The organic solvent waste (over 100 l) generated by the HPLC method would have then been reduced to approx. 1.272 l, a considerable time and cost savings in waste management.

- IT 55837-20-2, Halofuginone  
 RL: ANT (Analyte); POL (Pollutant); ANST (Analytical study); OCCU (Occurrence)  
 (halofuginone in chicken liver determined by competitive ELISA and HPLC)
- RN 55837-20-2 HCPLUS
- CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1991		HLF-1	Analytical Chemistry	
Anon	1995		201.8	Chemical Economics H	
Anon	1997			Estimate of US marke	
Anon	1985	50	33718	Federal Register	
Anon	1991	4	54	Food Chemical News	
Anon	1997			World wide use of co	
Beier, R	1996	8	11	Food and Agricultura	HCPLUS
Beier, R	1998	46	1049	Journal of Agricultu	HCPLUS
Beier, R	1994	17	2961	Journal of Liquid Ch	HCPLUS
Brown, J	1995			Compound evaluation	
Cheng, C	1976	59	497	Journal of Theoretic	HCPLUS
Karu, A	1991	451	59	ACS Symposium Series	
McDougald, L	1990		307	Coccidiosis of Man a	
Openshaw, H	1953	III	101	The Alkaloids	
Rowe, L	1994	42	1132	Journal of Agricultu	HCPLUS
Rowe, L	1993	23	2191	Synthetic Communicat	HCPLUS
Shepard, M	1996		5.289	The Complete Handboo	
Staros, J	1986	156	220	Analytical Biochemis	HCPLUS
Sundlof, S	1992			Food Animal Residue	

L32 ANSWER 20 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2002:461765 HCPLUS

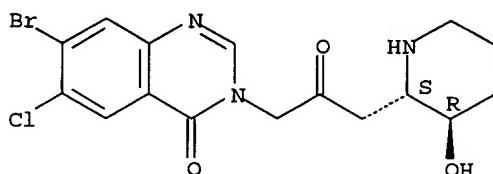
DN 138:66342

TI Analysis of the effect of halofuginone on bleomycin-induced scleroderma

AU Yamamoto, T.; Nishioka, K.

CS Department of Dermatology, School of Medicine, Tokyo Medical and Dental University, Tokyo, 113-8519, Japan  
 SO Rheumatology (Oxford, United Kingdom) (2002), 41(5), 594-596  
 CODEN: RUMAFK; ISSN: 1462-0324  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB The inhibitory effect of halofuginone administered along with bleomycin on the induction of dermal sclerosis was evaluated using a mouse model. S.c. nor i.p. administration of halofuginone failed to inhibit the dermal sclerosis induced by bleomycin. Daily i.p. injections of halofuginone together with s.c. injections of bleomycin for three weeks did not attenuate the dermal sclerosis in mouse model. S.c. injections of 0.1 µg/mL halofuginone along with bleomycin slightly moderated the dermal sclerosis but did not prevent its occurrence. Simultaneous treatment with halofuginone and bleomycin did not produce a considerable reduction in the collagen content.  
 IT 55837-20-2, Halofuginone  
 RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (effect of halofuginone on bleomycin-induced scleroderma)  
 RN 55837-20-2 HCPLUS  
 CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adamson, I	1984	55	25	Environ Health Persp	HCPLUS
Aso, Y	1976	35	558	Lab Invest	HCPLUS
Chandler, D	1990	11	21	Clin Chest Med	MEDLINE
Choi, E	1995	130	257	Arch Surg	MEDLINE
Clark, J	1980	631	359	Biochem Biophys Acta	HCPLUS
Cutroneo, K	1986	89	121S	Chest	HCPLUS
Granot, I	1993	1156	107	Biochim Biophys Acta	HCPLUS
Granot, I	1991	70	1559	Poult Sci	HCPLUS
Jimenez, S	1994	12	425	Clin Dermatol	MEDLINE
Kelley, J	1985	131	836	Biochem Biophys Res	HCPLUS
Krieg, T	1988	18	457	J Am Acad Dermatol	MEDLINE
LeRoy, E	1988	15	202	J Rheumatol	MEDLINE
Levi-Schaffer, F	1996	106	84	J Invest Dermatol	HCPLUS
Nagler, A	1996	154	1082	Am J Respir Crit Car	MEDLINE
Sterling, K	1983	258	14438	J Biol Chem	HCPLUS
Yamamoto, T	2000	292	535	Arch Dermatol Res	MEDLINE
Yamamoto, T	2000	292	556	Arch Dermatol Res	HCPLUS
Yamamoto, T	1999	112	456	J Invest Dermatol	HCPLUS
Yamamoto, T	2001	117	999	J Invest Dermatol	HCPLUS
Yamamoto, T	1999	26	2628	J Rheumatol	MEDLINE

L32 ANSWER 21 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN

AN 1966:75106 HCPLUS

DN 64:75106

OREF 64:14028d-e

TI Colorimetric method for determination of febrifugine and isofebrifugine

AU Li, Lu-Hsien; Ou, Chia-Wei; Hsieh, Shu-Min

SO Huaxue Xuebao (1965), 31(6), 482-5  
 CODEN: HHHPA4; ISSN: 0567-7351  
 DT Journal  
 LA Chinese  
 AB The method described is based on the principle that o-aminobenzoic acid is produced by alkaline hydrolysis of the quinazolone structure of the febrifugine (I) or isofebrifugine (II) mol., which can be determined colorimetrically by coupling with N-(1-naphthyl)ethylene-diamine after diazotization. The optical d.-concentration curve of the II hydrolyzate coincided with that of pure o-aminobenzoic acid and followed Beer's Law. An anal. procedure was established after systematic examination of the conditions of hydrolysis and color formation. The sensitivity of detection as expressed by the optical d. at 530 m $\mu$ / $\gamma$  of II/ml. of colored solution was 0.111/ $\gamma$ /ml. The total content of I and II of the leaves of a sample of Dichroa febrifuga was found to be 0.71% by this method. By means of this method, it was shown that the yield from CHCl<sub>3</sub> extraction is <50%

L32 ANSWER 22 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1966:75105 HCPLUS  
 DN 64:75105  
 OREF 64:14028c-d  
 TI Identification of choline in preparations of Viscum album by paper chromatography  
 AU Revyatskaya, A. P.  
 CS Med. Inst., Lvov

SO Farmatsevtichnii Zhurnal (Kiev) (1965), 20(6), 27-30  
 CODEN: FRZKAP; ISSN: 0367-3057  
 DT Journal  
 LA Ukrainian  
 AB Infusions of V. album in 70, 40, and 20% alc. were studied by ascending paper chromatography, using the systems BuOH-AcOH-H<sub>2</sub>O (4:1:5), BuOH-EtOH-AcOH-H<sub>2</sub>O (8:2:1:3) and BuOH-AcOH (1:3) saturated with H<sub>2</sub>O. In all these systems the infusions behaved similarly and their R<sub>f</sub> were identical with that of choline chloride (0.24, 0.40, and 0.43, resp.). The highest concentration of choline chloride was obtained by extraction with 40% alc.

L32 ANSWER 23 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1965:431884 HCPLUS  
 DN 63:31884  
 OREF 63:5702f-h  
 TI The structure of retamine and the partial synthesis of the (-)-enantiomorph  
 AU Shin, Kju Hi; Fonzes, L.; Marion, Leo  
 CS Natl. Res. Council, Ottawa  
 SO Canadian Journal of Chemistry (1965), 43(7), 2012-16  
 CODEN: CJCHAG; ISSN: 0008-4042

DT Journal  
 LA English  
 AB Previous work by many authors has led to the assumption that retamine might be (+)-12-hydroxysparteine. A partial synthesis of the enantiomorph of this compound has been effected by dehydration of (+)-13-hydroxylupanine and hydroboration of the product. The dehydration product consisted of two components that were separated by thin-layer chromatography and identified by the characteristics of their nuclear magnetic resonance spectra as  $\Delta$ 12,13 and  $\Delta$ 13,14-dehydrolupanine. Hydroboration of the  $\Delta$ 12,13-isomer gave rise to (-)-12-hydroxysparteine having, in thin-layer chromatography, the same R<sub>f</sub> value as natural retamine and the same optical rotation numerically, although of opposite sign. The synthetic base had the same infrared and n.m.r. spectra as the alkaloid and the two had superimposable Debye-Scherrer patterns. Evidence is given showing the hydroxyl to be equatorial.

L32 ANSWER 24 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1965:431883 HCPLUS

DN 63:31883  
 OREF 63:5702f  
 TI The absolute configuration of febrifugine. The absolute configuration of methyl jasmonate. Asymmetric induction in the Claisen rearrangement  
 AU Edwards, Anthony Gilbert  
 CS Princeton Univ., Princeton, NJ  
 SO (1965) 174 pp. Avail.: Univ. Microfilms (Ann Arbor, Mich.), Order No. 65-2127  
 From: Dissertation Abstr. 25(10), 5557  
 DT Dissertation  
 LA English  
 AB Unavailable

L32 ANSWER 25 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1965:431882 HCPLUS  
 DN 63:31882  
 OREF 63:5702e-f  
 TI Synthesis of Vinca minor alkaloids  
 AU Kuehne, Martin E.  
 CS Univ. of Vermont, Burlington  
 SO Lloydia (1964), 27(4), 435-9  
 CODEN: LLOYA2; ISSN: 0024-5461  
 DT Journal  
 LA English  
 AB cf. CA 61, 9546f. A lecture on the total synthesis of dl-vincamine with 14 references.

L32 ANSWER 26 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1964:443286 HCPLUS  
 DN 61:43286  
 OREF 61:7551f-g  
 TI Inhibition of tumor growth with antimetabolites of hexose monophosphate pathway intermediates  
 AU Sahasrabudhe, M. B.; Narurkar, M. V.; Kotnis, L. B.  
 CS At. Energy Estab., Bombay  
 SO Acta Unio Internationalis contra Cancrum (1964), 20(1-2), 221-5  
 CODEN: AICCA6; ISSN: 0365-3056  
 DT Journal  
 LA English  
 AB A group of 38 compds. modeled as antimetabolites of 6-phosphogluconic acid, sedoheptulose 7-phosphate, and erythrose 4-phosphate were tested against Yoshida ascites sarcoma in rats and solid fibrosarcoma in Swiss mice. Compds. displaying activity were 2,5-dicarboxythiophene, 2,5-bis(mercaptomethyl)thiophene, a thiouronium derivative of 2,5-bis(chloromethyl)thiophene, 2,5-dicarbethoxy-3,4-dihydroxythiophene (I), thiodiglycolic acid, thiodiglycol, and thiadipropionic acid. I and thiadiglycolic acid were tried clin. without spectacular results.

L32 ANSWER 27 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1964:443285 HCPLUS  
 DN 61:43285  
 OREF 61:7551e-f  
 TI Search for antitumor substances of plant origin  
 AU Vermel, E. M.  
 SO Acta Unio Internationalis contra Cancrum (1964), 20(1-2), 211-13  
 CODEN: AICCA6; ISSN: 0365-3056  
 DT Journal  
 LA English  
 AB Peucedanin, xanthotoxin, and prangenicin given orally in oil in doses of 50-70 mg./kg. inhibited Ehrlich ascites tumor growth. Hydropeucedanin, imperatorin, and bergapten were less active. These furocoumarins increased the therapeutic effect of tris(1-aziridinyl)phosphine sulfide. Peucedanin orally and topically was an effective adjunct to human therapy, and gossypol applied topically had a marked lytic effect on ulcerated melanomas but no toxic effect on normal or granuloma tissue.

- L32 ANSWER 28 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1962:436250 HCAPLUS  
 DN 57:36250  
 OREF 57:7219e-g  
 TI Absolute configuration of febrifugine  
 AU Hill, R. K.; Edwards, A. G.  
 CS Princeton Univ., Princeton, NJ  
 SO Chemistry & Industry (London, United Kingdom) (1962) 858  
 CODEN: CHINAG; ISSN: 0009-3068  
 DT Journal  
 LA Unavailable  
 AB Alkaline KMnO<sub>4</sub> oxidation of (-)-Nbenzoyl-β-furyl-β-alanine gave L(+) -N-benzoylaspartic acid- (I), identified by the infrared spectrum (in CCl<sub>4</sub>) of its di-Me ester. Although most (2/3) of the product was racemized, the optical activity, [α]D<sub>20</sub> 13.2° (dilute alkaline), was sufficient to assign I the S configuration. Since the substituents on the piperidine ring of febrifugine (II) were cis, natural (+)-II had the (2S,3S) configuration. Comparison of I with other natural β-hydroxypiperidines showed that the OH group had the same absolute configuration as pseudoconhydrine. The configuration was enantiomeric, however, with those of δ-hydroxylysine and 5-hydroxypipeolic acid
- L32 ANSWER 29 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1962:436249 HCAPLUS  
 DN 57:36249  
 OREF 57:7219d-e  
 TI α-Substituted sulfides. VIII. Introduction of the trichloromethylthio group in to the 3-position of cyclic ethers  
 AU Senning, Alexander; Lawesson, Sven Olov  
 CS Univ. Uppsala, Swed.  
 SO Acta Chem. Scand. (1961), 15, 1203  
 DT Journal  
 LA German  
 OS CASREACT 57:36249  
 AB cf. preceding abstract 2-Ethoxy-3-(trichloromethylthio)- tetrahydrofuran (I) was prepared by adding slowly CCl<sub>3</sub>SO<sub>2</sub>Cl with stirring to concentrated HCl and EtOH. The mixture was dissolved in Et<sub>2</sub>O, shaken with NaHCO<sub>3</sub> solution and water, dried over MgSO<sub>4</sub>, and distilled under reduced pressure to give I, b15 135-42°
- L32 ANSWER 30 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1958:2195 HCAPLUS  
 DN 52:2195  
 OREF 52:460d-f  
 TI Sulfonamides  
 IN Mueller, Paul; Trefzer, Robert  
 PA Ciba Pharmaceutical Products, Inc.  
 DT Patent  
 LA Unavailable  
 FAN.CNT 1
- | PATENT NO.      | KIND  | DATE     | APPLICATION NO. | DATE     |
|-----------------|-------|----------|-----------------|----------|
| -----           | ----- | -----    | -----           | -----    |
| PI US---2792391 |       | 19570514 | 1955US-0514366  | 19550609 |
- AB N1-Heterocyclic-substituted-p-aminobenzenesulfonamides are prepared by treating a benzenesulfonyl halide with 6-amino-2,4-dimethylpyrimidine (I) or 2-aminothiazole (II) in the presence of a condensing agent. I (60 g.) and 171 g. dry p-AcNH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl (III) introduced into 800 cc. PhNO<sub>2</sub> with stirring at 20-5°, 65 g. Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> (IV) added dropwise over 6 hrs. at an internal temperature of 45° with the exclusion of moisture, the yellow solution stirred 15 hrs. at 40-5°, 600 g. 30% NaOH solution added slowly, the mixture heated with stirring 2 hrs. at 90°, cooled to 30-40°, the precipitated Na salt separated, washed with 30% NaOH solution and 300 cc. fresh PhNO<sub>2</sub>, the residue taken up in 1000 cc. H<sub>2</sub>O, the PhNO<sub>2</sub> removed by azeotropic distillation in vacuo with the H<sub>2</sub>O distilled continuously replaced, and the remaining aqueous solution filtered hot with animal C and neutralized with HCl gives 70% 6-(p-aminobenzenesulfonamido)-2,4-

dimethylpyrimidine. Similarly III, II, and IV give 87%  
2-(p-aminobenzenesulfonamido)thiazole.

L32 ANSWER 31 OF 31 HCPLUS COPYRIGHT 2006 ACS on STN

AN 1958:2194 HCPLUS

DN 52:2194

OREF 52:4591,460a-d

TI Quinazolinones

IN Baker, Bernard R.; Querry, Merle V.

PA American Cyanamid Co.

DT Patent

LA Unavailable

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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✓ PI US---2796417 19570618 1952US-0280384 19520403

AB ( $\beta$ -Oxoalkyl)quinazolinones are prepared by adding 1-carbethoxy-2-( $\gamma$ -bromoacetyl) piperidine to a solution of a sodioquinazolone. A mixture of 7 g. NaOMe, 100 ml. MeOH, and 20.6 g. 3-chloro-3-carbethoxy-2-piperidone refluxed and acidified gave 3-methoxy-3-carbomethoxy-2-piperidone (I), b0.15 142-50°, m. 79.5-80°. I (36.4 g.) and 122 ml. 6N HCl refluxed, the crude  $H_2N(CH_2)_3CH(OMe)CO_2H \cdot HCl$  dissolved in a solution of 430 ml. H<sub>2</sub>O and 37.3 g. NaOH, and 60 ml. ClCO<sub>2</sub>CH<sub>2</sub>Ph added dropwise at 8° gave PhCH<sub>2</sub>O<sub>2</sub>CNH(CH<sub>2</sub>)<sub>3</sub>CH(OMe)CO<sub>2</sub>H, (II), m. 63-5°. PC15 (67 g.) added portionwise to 83 g. II in 200 ml. AcCl in 7 min., and the acid chloride treated with 141 g. CH<sub>2</sub>(CO<sub>2</sub>Et)<sub>2</sub>, 66.1 g. Mg(OMe)<sub>2</sub>, and 300 ml. PhMe and acidified gave Et (2-methoxy-5-carbobenzoyloxyaminovaleryl) malonate (III). III (25 g.) in 75 ml. HOAc hydrogenated with Pd-C and then Pt catalysts, the crude product refluxed with 128 ml. 6N HCl, cooled, 42 ml. H<sub>2</sub>O added, and the mixture treated with 74 ml. 10% NaOH and 6.2 ml. ClCO<sub>2</sub>Et in 30 ml. PhMe gave 5 g. (1-carbethoxy-3-methoxy-2-piperidyl) acetic acid (IV). IV (5.3 g.) in 25 ml. AcCl treated with 5.1 g. PC15, evaporated to dryness, the residue dissolved in 33 ml. C<sub>6</sub>H<sub>6</sub>, added to CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O [from 13 g. Me(NO)NCONH<sub>2</sub>], allowed to stand 17 hrs., HOAc and HBr added, and the solvent evaporated gave 5 g. 1-carbethoxy-2-( $\gamma$ -bromoacetyl)-3-methoxypiperidine (V). V (5.1 g.) in 51 ml. MeOH added to 2.15 g. 4-quinazolinone in 15 ml. N NaOMe in MeOH, the mixture diluted after 1 hr. at room temperature with 205 ml. H<sub>2</sub>O and 82 ml. 10% NaOH gave a gum which yielded 3-[ $\beta$ -oxo- $\gamma$ -(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-4-quinazolinone. Similarly other 3-[ $\beta$ -oxo- $\gamma$ -(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-substituted 4-quinazolinones were prepared (substituents given): 6-Cl, m. 124-5°; 6-Me, m. 113-15°; 6-MeO, m. 102-3°; 8-Cl, m. 153-4°; 8-Me, m. 125-6°; 5-Cl, 8-MeO. All the following were gums: 5-Me, 5-Cl, 5-Br, 5,6-Cl<sub>2</sub>Me, 5,6-di-Me, 5-CF<sub>3</sub>, 5-MeO, 5-F. 3-[ $\beta$ -Oxo- $\gamma$ -(1-benzoyl-2-piperidyl)propyl]-4-quinazolinone-HCl and 3-[ $\beta$ -oxo- $\gamma$ -(1-carbethoxy-3-phenoxy-2-piperidyl)propyl]-4-quinazolinone are also reported. The compds. are useful as intermediates for preparing antimalarial materials.

=> b hcao

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=> d all 129 tot

L29 ANSWER 1 OF 5 HCAOLD COPYRIGHT 2006 ACS on STN  
 AN CA64:14028d CAOLD  
 TI colorimetric method for determination of febrifugine and isofebrifugine  
 AU Li, Lu-Hsien; Ou, C. W.; Hsieh, S. M.  
 IT 486-68-0 496-32-2 24159-07-7 32434-44-9

L29 ANSWER 2 OF 5 HCAOLD COPYRIGHT 2006 ACS on STN  
 AN CA63:5702f CAOLD  
 TI absolute configuration of febrifugine-of methyl jasmonate-asym. induction in the Claisen rearrangement  
 AU Edwards, Anthony G.  
 TI structure of retamine and the partial synthesis of the (-)-enantiomorph  
 AU Shin, Kju Hi; Fonzes, L.; Marion, L.  
 IT 2122-29-4 2122-40-9 2122-41-0 3300-52-5 24159-07-7  
 27804-79-1 39924-52-2

L29 ANSWER 3 OF 5 HCAOLD COPYRIGHT 2006 ACS on STN  
 AN CA61:7551f CAOLD  
 TI inhibition of tumor growth with antimetabolites of hexose monophosphate pathway intermediates  
 AU Sahasrabudhe, M. B.; Narurkar, M. V.; Kotnis, L. B.  
 IT 123-93-3 1822-66-8 4282-31-9 14282-62-3 24159-07-7  
 97197-96-1

L29 ANSWER 4 OF 5 HCAOLD COPYRIGHT 2006 ACS on STN  
 AN CA57:7219e CAOLD  
 TI absolute configuration of febrifugine  
 AU Hill, Richard K.; Edwards, A. G.  
 IT 24159-07-7

L29 ANSWER 5 OF 5 HCAOLD COPYRIGHT 2006 ACS on STN  
 AN CA52:460d CAOLD  
 TI sulfonamides  
 AU Mueller, Paul; Trefzer, R.  
 PA Ciba Pharmaceutical Products Inc.  
 DT Patent  
 PATENT NO. KIND DATE  
 -----  
 PI US---2792391 1957  
 IT 342-50-7 387-16-6 102551-75-7 102701-36-0 103168-77-0 111163-09-8  
 111163-10-1 114697-26-6

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 DICTIONARY FILE UPDATES: 18 SEP 2006 HIGHEST RN 907539-37-1

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**TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006**

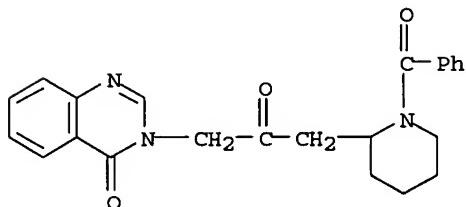
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<http://www.cas.org/ONLINE/UG/regprops.html>

=> d ide can l30 tot

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L30 ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN 114697-26-6  REGISTRY
ED Entered STN: 04 Jun 1988
CN 4(3H)-Quinazolinone, 3-[3-(1-benzoyl-2-piperidyl)acetyl]-, hydrochloride
     (6CI) (CA INDEX NAME)
MF C23 H23 N3 O3 . Cl H
SR CAOLD
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
     (*File contains numerically searchable property data)
CRN (807287-73-6)
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● HCl

3 REFERENCES IN FILE CA (1907 TO DATE)  
 3 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 52:2194

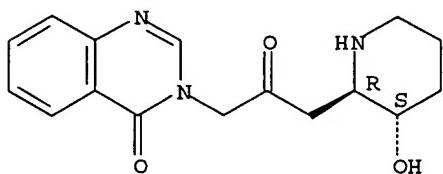
REFERENCE 2: 49:84525

REFERENCE 3: 46:60683

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L30 ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN 24159-07-7  REGISTRY
ED Entered STN: 16 Nov 1984
CN 4(3H)-Quinazolinone, 3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-
     (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Febrifugine (7CI, 8CI)
OTHER NAMES:
CN (+)-Febrifugine
CN β-Dichroin
```

CN  $\beta$ -Dichroine  
 CN Dichroin B  
 CN NSC 315535  
 CN trans- (+)-Febrifugine  
 FS STEREOSEARCH  
 DR 880384-80-5, 732982-92-2, 486-68-0  
 MF C16 H19 N3 O3  
 CI COM  
 LC STN Files: AGRICOLA, BEILSTEIN\*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT,  
     CHEMCATS, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK\*, NAPRALERT, RTECS\*,  
     TOXCENTER, USPAT2, USPATFULL  
     (\*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

79 REFERENCES IN FILE CA (1907 TO DATE)  
 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 79 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 144:331601  
 REFERENCE 2: 144:107626  
 REFERENCE 3: 143:440273  
 REFERENCE 4: 143:128444  
 REFERENCE 5: 142:355444  
 REFERENCE 6: 142:348229  
 REFERENCE 7: 141:277798  
 REFERENCE 8: 141:64433  
 REFERENCE 9: 140:104489  
 REFERENCE 10: 140:70980

=> d his

(FILE 'HOME' ENTERED AT 16:49:29 ON 19 SEP 2006)

FILE 'HCAPLUS' ENTERED AT 16:49:36 ON 19 SEP 2006  
 L1 1 US2004053950/PN OR (US2003-600446 OR US2002-390334#) /AP, PRN  
     E JIANG S/AU  
 L2 641 E3-23  
     E JIANG SUPING/AU  
 L3 15 E3  
     E JIANG SU/AU

L4            E HUDSON T/AU  
       60 E3-18  
       E HUDSON TOM/AU  
 L5            9 E3-5  
       E HUDSON THOM/AU  
 L6            167 E4-13  
       E MILHOUS W/AU  
 L7            118 E3-8

FILE 'REGISTRY' ENTERED AT 16:52:22 ON 19 SEP 2006

FILE 'HCAPLUS' ENTERED AT 16:52:22 ON 19 SEP 2006  
 L8            TRA L1 1- RN :        16 TERMS

FILE 'REGISTRY' ENTERED AT 16:52:22 ON 19 SEP 2006

L9            16 SEA L8  
 L10          11 L9 AND NCNC3-C6/ES  
 L11          5 L9 NOT L10  
 L12          30096 (NCNC3-C6 OR OCOC2-NCNC3-C6)/ES AND NC5/ES  
 L13          92 L12 AND (C16H19N3O3 OR C16H17BRCLN3O3 OR C16H16CL3N3O3 OR C16H1  
 L14          23 L12 AND (C17H19BRCLN3O3 OR C18H21N3O5 OR C18H21N3O5 OR C22H27N3  
 L15          115 L13-14  
 L16          STR  
 L17          4 L16 SAM SUB=L15  
 L18          85 L16 FULL SUB=L15  
               SAV TEM L18 KAN446F0/A

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FILE 'REGISTRY' ENTERED AT 17:08:50 ON 19 SEP 2006  
       SEL RN 1-2 10-11 14-19 21-34 36 39 45 53-72 74-76 82 84-85  
 L19          53 L18 AND E1-53

FILE 'HCAPLUS' ENTERED AT 17:16:48 ON 19 SEP 2006

L20          374 L19  
 L21          2 L20 AND L1-7  
 L22          372 L20 NOT L21  
 L23          255 L22 AND PHARM?/SC,SX  
 L24          289 L22-23 AND (PY<=2002 OR AY<=2002 OR PRY<=2002)  
 L25          62 L24 AND P/DT  
       SEL AN 1-10  
 L26          10 L25 AND E54-73  
       DEL SEL Y  
 L27          227 L24 NOT L25  
       SEL AN 1-10 L27  
 L28          10 E1-20 AND L27

FILE 'HCAOLD' ENTERED AT 17:20:41 ON 19 SEP 2006  
 L29          5 L19  
       SEL HIT RN L29

FILE 'REGISTRY' ENTERED AT 17:21:01 ON 19 SEP 2006  
 L30          2 E21-23

FILE 'HCAOLD' ENTERED AT 17:21:18 ON 19 SEP 2006  
       SEL AN L29  
       EDIT /AN /OREF

FILE 'HCAPLUS' ENTERED AT 17:21:38 ON 19 SEP 2006  
 L31          11 E24-28  
 L32          31 L26,L28,L31

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